Pancreatology

International Consensus Guidelines on Surveillance for Pancreatic Cancer in Chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association Of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club

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Abstract:	Background Patients with chronic pancreatitis (CP) have an increased risk of pancreatic cancer. We present the international consensus guidelines for surveillance of pancreatic cancer in CP. Methods The international group evaluated 10 statements generated from evidence on 5 questions relating to pancreatic cancer in CP. The GRADE approach was used to evaluate the level of evidence available per statement. The working group voted on each statement for strength of agreement, using a nine-point Likert scale in order to calculate Cronbach's alpha reliability coefficient. Results In the following domains there was strong consensus: (1) the risk of pancreatic cancer in affected individuals with hereditary pancreatitis due to inherited PRSS1 mutations is high enough to justify surveillance; (2) the risk of pancreatic cancer in patients with CP associated with SPINK1 p. N34S is not high enough to justify surveillance; (3) surveillance should be undertaken in pancreatic specialist centers; (4) surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention. All patients with CP should be advised to lead a healthy lifestyle aimed at avoiding risk factors for progression of CP and pancreatic cancer. There was only moderate or weak agreement on the best methods of screening and surveillance in other types of environmental, familial and genetic forms of CP. Conclusions Patients with inherited PRSS1 mutations should undergo surveillance for pancreatic cancer, but the best methods for cancer detection need further investigation.
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Dear Miklós,

On behalf of all of the co-authors I would be grateful if this Guideline, part of the ICGCP set of Guidelines be considered for publication in Pancreatology. We have worked on this for the best part of three years.

I can confirm that the work is original and free from plagiarism; it has not been submitted for publication and is not under consideration for publication at another Journal; and all authors have approved the final version and are aware of the order of authorship.

With best wishes,

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ABSTRACT

Background: Patients with chronic pancreatitis (CP) have an increased risk of pancreatic cancer. We present the international consensus guidelines for surveillance of pancreatic cancer in CP.

Methods: The international group evaluated 10 statements generated from evidence on 5 questions relating to pancreatic cancer in CP. The GRADE approach was used to evaluate the level of evidence available per statement. The working group voted on each statement for strength of agreement, using a nine-point Likert scale in order to calculate Cronbach's alpha reliability coefficient.

Results: In the following domains there was strong consensus: (1) the risk of pancreatic cancer in affected individuals with hereditary pancreatitis due to inherited *PRSS1* mutations is high enough to justify surveillance; (2) the risk of pancreatic cancer in patients with CP associated with *SPINK1* p. N34S is not high enough to justify surveillance; (3) surveillance should be undertaken in pancreatic specialist centers; (4) surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention. All patients with CP should be advised to lead a healthy lifestyle aimed at avoiding risk factors for progression of CP and pancreatic cancer. There was only moderate or weak agreement on the best methods of screening and surveillance in other types of environmental, familial and genetic forms of CP.

Conclusions: Patients with inherited *PRSS1* mutations should undergo surveillance for pancreatic cancer, but the best methods for cancer detection need further investigation.

INTRODUCTION

Chronic pancreatitis is a complex inflammatory disease with pain as the most dominant symptom.[1] Pancreatic ductal adenocarcinoma (PDAC) can arise against a background of chronic pancreatitis although the relative risk varies considerably, in part because of other contributing factors including the duration of the disease, tobacco consumption, excess alcohol consumption, diet and physical activity, and late onset diabetes melitus.[2] Mechanistically ongoing pancreatic parenchymal chronic inflammation is related to the acquisition of somatic *KRAS* mutations in pancreatic ductal cells and the development of pancreatic intraepithelial neoplasms, progressing to PDAC.[3] Chronic pancreatitis can also promote acinar-to-ductal metaplasia, which has been linked to development of PDAC.[4] The incidence of pancreatic cancer is approximately 10 per 10^5 per year with a slightly higher prevalence of around 12 per 10^5 whilst the incidence and prevalence of chronic pancreatitis are estimated at 5-12 per 10^5 per year and 50 per 10^5 respectively.[5-11] The pooled relative risk estimates for pancreatic cancer among patients with CP varies from 2.7 to 13.3.[12-15] Among all risk factors associated with pancreatic cancer, CP has the highest relative risk (RR) of greater than 2, with lower risk RR (<2) for tobacco smoking, diabetes mellitus (not treated with metformin), family history or metabolic syndrome.[16] However, subsets of subjects with family history of pancreatic cancer or those with new-onset diabetes over age 50 years have much higher risks. Similarly, subsets of CP cohorts have markedly elevated risk of pancreatic cancer.[17,18] Thus, guidelines on screening for pancreatic cancer in CP patients with the highest relative risk are important.

Unlike sporadic chronic pancreatitis, the risk of PDAC in patients with autosomal dominant hereditary chronic pancreatitis, where the disease is due to gain-of-function mutations in the protease serine 1 (*PRSS1*) gene (e.g. p.N29I, p.R122H, p.A16V), appears to be much greater, with a relative risk of up to 87. [19-24] A study of patients with CP from Madras (tropical pancreatitis had an estimated relative risk of 100.[25] Cystic fibrosis transmembrane conductance

regulator (CFTR) mutations in patients with chronic pancreatitis are also associated with a small increased relative risk of PDAC.[26-30] There is no established direct association however, between other inherited genes, variants or polymorphisms in patients with chronic pancreatitis linked to pancreatic cancer including a the serine protease inhibitor Kazal type 1 (*SPINK1*), chymotrypsin C (*CTRC*), or carboxyl-ester lipase (*CEL*).[30-38] A study by Muller et al however identified a hazard ratio of 12.0 of PDAC in patients with pancreatitis carrying *SPINK1* variants compared to patients with idiopathic pancreatitis but with a wide 95% confidence interval (CI) of 3.0-47.8.[39]

The key determinants for screening are the prevalence of the disease, the accuracy of the screening methodology and the cost-benefit ratio of the screening.[40,41] The prevalence of pancreatic cancer, is not high enough *per se* to justify general (primary) screening of the adult population. [40,41] The fundamental requirement for screening is for the true positive to false positive (TP:FP) ratio to be $\geq$1.0, since the proportion of false positives must not exceed that of true positives to a great extent. [40] If the TP:FP ratio is greatly below 1.0, then any benefit derived from screening is lost due to the excess morbidity and mortality. Assuming the prevalence of the at-risk population is 10 per 10^5 of the general adult population and the sensitivity and specificity of the conventional screening modalities for pancreatic cancer to be 85%, then the TP:FP ratio is only 6 per 10^{-4}, resulting in 1,764 false positives for each true positive.[40]

Although several different treatment guidelines on chronic pancreatitis exist, the aim was to create a consensus guideline that is truly international and multidisciplinary, covering from development and early diagnosis to progression and treatment of chronic pancreatitis. To develop the first international guidelines on chronic pancreatitis, John Neoptolemos, David Whitcomb, Carlos Fernandez-Del Castillo, and Tooru Shimosegawa started at the European Pancreas Club (EPC) 2016 meeting on a joint venture with endorsement from the international

societies: International Association of Pancreatology (IAP), American Pancreatic Association (APA), Japan Pancreas Society (JPS) and the European Pancreatic Club (EPC). International experts were identified to have a multidisciplinary representation within subgroups focusing on 16 key topics of chronic pancreatitis. The first major step was the agreement on a new mechanistic definition of chronic pancreatitis.[1] Thereon several other parts of the consensus guidelines were published, covering the early diagnosis of chronic pancreatitis, imaging of chronic pancreatitis and understanding and management of pain.[42-44] This manuscript is another part of the international consensus guidelines, covering the topic on screening for pancreatic cancer in chronic pancreatitis.

METHODS

A team of 25 worldwide experts on pancreatic cancer surveillance in chronic pancreatitis with WG appointed as chair of the group. In 2016 the Presidents of the IAP, APA, JPS and EPC agreed to develop International Consensus Guidelines for Chronic Pancreatitis in collaboration with members of the respective organisations. The initial series of meetings occurred EPC 48th Annual Meeting, Liverpool UK, 6th -9th July 2016; 20th Scientific Meeting of the IAP in conjunction with the 47th Annual Meeting of the JPS and the 6th Meeting of the Asian- Oceanic Pancreatic Association. August 4th – 8th, 2016, Sendai International Center, Japan; APA, 47th Annual Meeting. Boston, MA, USA, 26th – 29th October 2016; PancreasFest 2017, Pittsburgh USA. July 28th 31st 2017; 21st IAP Meeting in conjunction with the Latin American Pancreatic Study Group (1st) Joint Meeting in Buenos Aires, Argentina, September 28-30, 2017. Based on a review of data from the relevant literature all experts presented their perspectives on the role of surgery and timing of intervention in the treatment of chronic pancreatitis. The method of the systematic literature review on articles on chronic pancreatitis was previously described.[39-41] The international experts evaluated 10 statements generated from evidence on 5

questions deemed to be the most clinically relevant on pancreatic cancer surveillance in chronic pancreatitis.

Grading

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the level of evidence per statement (see http://www.uptodate.com/home/gradingtutorial). Quality assessment of evidence was graded as 'high' if there was (very) low probability of further research substantially changing the conclusions, 'moderate' if further research might completely change the conclusions, and 'low' if further research was likely to completely change the conclusions. The strengths of the recommendation were graded as 'strong' if it was very certain that benefits outweigh risks and burdens, 'weak' if risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain, or 'conditional' if it was in between strong and weak recommendation.

Consensus

After grading, the working group of international experts voted on the 10 statements for strength of agreement, using a nine-point Likert scale. Out of the results, a Cronbach's alpha reliability coefficient was calculated per statement (http://hdl.handle.net/1805/344). The voting results were classified for agreement as either; 'strong' if 80% of votes were 7 or above, 'conditional' if 65% of votes were 7 or above, and 'weak' if less than 65% of votes were 7 or above. In addition, comments to each question and statements were compiled to explain the surrounding issues, supported by key references. An overview of results from the most important studies were tabulated and presented in the supplementary appendix. All statements and comments were reviewed by all authors to ensure the general relevance and applicability of the conclusions. Eventually a final draft of the document was generated and circulated to all authors for final editing and approval.

RESULTS

Question 1: Should all patients with chronic pancreatitis undergo screening or surveillance for pancreatic cancer?

Statement 1.1: The prevalence of pancreatic cancer in sporadic chronic pancreatitis is not high enough to justify screening or surveillance.

Quality assessment: High; Recommendation: Conditional; Agreement: **(α= 74%).**

Statement 1.2: The risk of pancreatic cancer in affected individuals with an autosomal dominant history of hereditary pancreatitis due to inherited *PRSS1* mutations is high enough to justify surveillance.

Quality assessment: High; Recommendation: Strong; Agreement: **(α= 83%).**

Statement 1.3: The risk of pancreatic cancer in affected individuals with an autosomal dominant history of hereditary pancreatitis but without *PRSS1* mutations is high enough to justify surveillance.

Quality assessment: Moderate; Recommendation: Weak; Agreement: **(α= 57%).**

Statement 1.4: The risk of pancreatic cancer in patients with chronic pancreatitis associated with *SPINK1* p. N34S is not high enough to justify screening or surveillance.

Quality assessment: Moderate; Recommendation: Strong; Agreement: **(α= 80%).**

Statement 1.5: The risk of pancreatic cancer in patients with chronic pancreatitis associated with other germline mutations including those of *CFTR, CTRC, CPA1*, and *CEL*, is not high enough to justify screening or surveillance.

Quality assessment: Moderate; Recommendation: Conditional; Agreement: **(α= 70%).**

Comment

The pooled relative risk estimates for pancreatic cancer among patients with sporadic chronic pancreatitis in two collective studies ranged from 2.7 to 13.3[12, 13] Duell *et al* analysed 10 case-control studies involving 5,048 cases of pancreatic cancer and 10,947 controls taking part in

the International Pancreatic Cancer Case-Control Consortium (PanC4). The association between chronic pancreatitis and pancreatic cancer (at intervals of >2 years between diagnoses) had an odds ratio of 2.71 (95% Confidence Interval [CI] = 1.96-3.74).[13] Bang *et al* using nationwide data from Danish registries from 1995 through 2010, evaluated 11,972 patients with CP and 71,814 person-years compared with 119,720 age- and sex-matched controls and 917,436 person-years observation.[45] A history of pancreatitis was associated with a hazard ratio for pancreatic cancer of 6.9 (95% CI: 5.6–8.6) .[45] Different estimations of pancreatic cancer risk based on multiple meta-analyses in patients with CP are summarized in Table 1.[12-15] Given the short life expectancy of pancreatic cancer patients the incidence tends to equal that of prevalence and thus this level of prevalence is insufficient for screening in patients with CP.[40]

The relative risk for pancreatic cancer in patients with autosomal dominant hereditary chronic pancreatitis due to *PRSS1* mutations is of up to 87 although the estimates are very wide.[19-24]

The risk of pancreatic cancer might be reduced by measures introduced to minimize the progression of chronic pancreatitis such as cessation of smoking and alcohol consumption as well as prophylactic total pancreatectomy in selected cases.[2,46-49]

Following a call to members of the APA and the IAP to participate in a longitudinal study of hereditary pancreatitis, 37 physicians from 10 countries contributed records of 246 patients with early age (≤30 years) symptom onset and a positive family history from April 1995 to February 1996.[19] Reporting in March 1997, there were eight new pancreatic cancers during 8,531 person-years of follow-up, with a standardized incidence ratio of 53 (95% CI = 23-105).[19] The estimated cumulative risk of pancreatic cancer to age 70 years was 40% (95% CI = 9-71%).[19]

A registry study based on families with sequenced *PRSS1* mutations by the European Registry of Hereditary Pancreatitis and Pancreatic Cancer EUROPAC) identified 418 affected individuals from 112 families in 14 countries, 58 (52%) families with the *PRSS1* p.R122H, 24

(21%) the *PRSS1* p.N29I, and 5 (4%) with the *PRSS1* p.A16V mutation, plus 2 with rare mutations, and 21 (19%) with no *PRSS1* mutation.[22] Participants in the registry were contacted prospectively on a regular basis. Three hundred seventy-five patients (from 111 families) with follow-up data were observed over an observation period of 14,064 person years with 20 (5%) pancreatic cancers being detected (1 cancer per 703 person years of follow-up).[22] The cumulative risk for pancreatic cancer was 44.0% (95% CI = 8.0-80.0%) at 70 years from symptom onset with a standardized incidence ratio of 67 (95% CI =50-82).[22]

An update of the EUROPAC study in 2010 reported a total of 37 pancreatic cancer cases amongst 652 affected individuals from 149 Hereditary Pancreatitis families; there were 19 PDAC cases amongst 336 affected individuals from 71 *PRSS1* p.R122H families; there were 10 PDAC cases amongst 157 affected individuals from 32 *PRSS1* p.N29I families; there were three PDAC cases amongst 19 affected individuals from 10 A16V families; and there was one PDAC case amongst 10 affected individuals from families with other *PRSS1* mutations.[50] Similar to the original report there were 10 PDAC cases amongst 134 affected individuals from 37 families with an autosomal dominant family history but without any *PRSS1* mutations or deleterious variants/mutations of the *SPINK1, CFTR* and *CTRC* genes.[50]

A study of patients living in France, was based on contacting all clinical gastroenterologists and pediatricians and genetics laboratories in the country from 2005 with response rates of 84% and 100% respectively.[23] Included in the analyses were 200 patients from 78 families with 6,673 person-years follow-up of whom 135 (67.5%) had a *PRSS1* mutation (p.R122H in 78%, p.N29I in 12%, and other mutations in 10%).[23] A pancreatic adenocarcinoma was diagnosed in ten patients (two were still alive at the census point) resulting in a cumulative risk at age 75 years were of 53.5% (95% CI = 7-76%).[23]

A recent study of USA patients organized from Pittsburgh, recruited 217 *PRSS1* carriers including 83.9% with *PRSS1* p.R122H and 11.5% with *PRSS1* p.N29I mutations from 1995–

2013.[24] Individual follow-up was not possible in all patients and so the Social Security Death Index (SSDI), and the National Death Index (NDI) through the National Center for Health Statistics (NCHS) were used to determine outcomes. Through this method they identified deaths in 37 *PRSS1* mutation carriers, five from pancreatic cancer with a standardized incidence ratio of 59 (95% CI = 19-138), and a cumulative risk at 70 years of 7.2% (95% CI = 0-15.4%).[24] The observation period in person years was not mentioned and actual number of cases of pancreatic cancer could not be determined. [24]

There are no tests currently available that could be regarded as screening tests and therefore diagnostic measures would be required for early detection. Carbohydrate antigen (CA)19-9, which has some utility in identifying pancreatic cancer in patients without pancreatitis, cannot be recommended in patients with CP as they often have raised CA19-9 in the absence of cancer, secondary to parenchymal inflammation.[51] The recent guidelines from the UK National Institute for Health and Care Excellence recommend that surveillance for pancreatic cancer is offered to people with hereditary pancreatitis and a *PRSS1* mutation.[52]

The relative risk of pancreatic cancer in patients with cystic fibrosis and/or *CFTR* mutation carriers with/or without chronic pancreatitis is significantly increased but less so than that in patients with hereditary pancreatitis from *PRSS1* mutations.[26-30] A study of 28,511 patients with cystic fibrosis from 1985 through 1992 in the United States and Canada identified 13 digestive tract cancers, during 164,764 person-years of follow-up, giving a ratio of observed to expected cancers of 6.5 (3.5 to 11.1) but there was only one case of pancreatic cancer.[26] As part of the same study the estimated numbers of patients with cystic fibrosis in 1992 as reported to the International Cystic Fibrosis Association, from 17 countries was approximately 24,500 with two cases of pancreatic cancer, giving an odds ratio of 31.5 with very wide confidence intervals (95 % CI = 4.8-205). [26] An analysis of nine patients with cystic fibrosis and pancreatic cancer identified from 1985 to 2006 reported from the USA, UK Germany, and Switzerland by

Maisonneuve *et al* was equivalent to an incidence of approximately 1 per 10^5 per year with a risk ratio of 5.3 (95% CI = 2.4-10.1).[28] They concluded that although the estimated risk of pancreatic cancer in cystic fibrosis was "greater than in the general population, compared with other causes of mortality, the absolute risk of pancreatic cancer in patients with cystic fibrosis is negligible".[28] A further study by Maisonneuve *et al* followed 41,188 patients who received care at 250 cystic fibrosis care center programs in the USA from 1990 to 2009, with 344,114 patient-years of observation of non-transplanted patients and found only one pancreatic cancer, giving standardized incidence ratio of 0.8 (95% CI = 0.0- 4.2).[53] A recent meta-analysis six cohort studies with 99,925 patients with cystic fibrosis providing 544,695 person-years by Yamada *et al*, found a pooled standardized incidence ratio for pancreatic cancer of 6-18 (95% CI= 1.31-29.27).[54] Maisonneuve *et al* commented that "the low absolute number of patients with cancer, the lack of a well-established screening test, and the high burden of additional testing do not support the strong screening recommendations for pancreatobiliary cancers made by Yamada and colleagues".[55]

McWilliams *et al* tested 949 patients with pancreatic cancer to see if they were also carriers of one or more of the 39 common cystic fibrosis-associated *CFTR* mutations and compared these to 13,340 case controls from a clinical laboratory database for prenatal testing for *CFTR* mutations.[29] Fifty (5.3%) of the patients with pancreatic cancer carried a common *CFTR* mutation compared to 510 (3.8%) of the controls, giving an odds ratio of 1.40 (95% CI = 1.04-1.89) and those with cancer more likely to be younger when diagnosed (<60 years), and more likely to be smokers.[29]

Nearly all studies have not shown any direct association however, between most other inherited genes, variants or polymorphisms in patients with CP linked to pancreatic cancer, including *SPINK1*, *CTRC*, and *CEL*.[30-38,53-56] A recent study combining 209 patients with pancreatitis and the *SPINK1* p.N34S variant from two France centers and one England center identified

seven cancers compared to three cancers in 302 patients with idiopathic pancreatitis (hazard ratio of 12.0, 95% CI = 3.0-47.8).[39]

Whilst variants in carboxypeptidase A1 (*CPA1*) have been identified in patients with chronic pancreatitis from Europe and India (although not in Han Chinese), and separately in patients with PDAC from high risk families, there is no direct evidence to link *CPA1* variants in chronic pancreatitis patients with a risk of PDAC.[55-59] Functionally impaired *CPA1* variants were found in 29/944 (3.1%) cases from Germany and in 5/3,938 (0.1%) matched controls, in 8/600 (1.3%) cases in a repeat set from Europe, and in 9/2,432 (0.4%) of their controls, from India in 5/230 (2.2%) cases and 0/264 controls, and from Japan in 5/247 (2.0%) cases and in 0/341 controls.[57] A study in Han Chinese found only three (0.27%) functionally impaired *CPA1* variants from 1,112 patients with idiopathic chronic pancreatitis versus two (0.13%) out of 1,580 in controls, but without a significant association.[58] Tamura and colleagues from John Hopkins University, identified *CPA1* variants in seven patients with PDAC from a combined set of hospital and familial pancreatic cancer cases compared with one in 2,012 controls giving an odds ratio of 9.36 (95% CI = 1.15-76.02).[59] The authors concluded that patients with *CPA1* variants could potentially benefit from pancreatic cancer screening and surveillance, but added that further investigation was needed to determine their lifetime risk of pancreatic cancer.[59] The recent evidence report for the US Preventive Services Task Force on screening identified 18 cases of PDAC in 1,317 high familial risk individuals from 13 studies, only 12 of which were at an early stage and noted that that there was no direct evidence of the effect of screening on morbidity or mortality.[60]

The relative risk of pancreatic cancer in patients with chronic pancreatitis in patients from India appears to be different from that in Europe and North America with differences in genetic and environmental risk factors.[61] In India *SPINK1* variants are associated with idiopathic chronic pancreatitis in 31.8-44% of cases, *CFTR* mutations in 9-32.6% of cases, *CTRC* mutations in

5.4-12.5% of cases and an odds ratio of 1.57-1.62 for the *MORC4/CLDN2* locus.[62] A study by Chari *et al* in 1994 followed 185 patients with chronic pancreatitis from the Diabetes Research Center in Madras, India for an average of 4.5 years.[25] There were six deaths from cancer of the pancreas (average age at onset of 45.6 +/- 7.3 years) with a relative risk of 100.2 (95% CI = 37-218).[25] A more recent study from the All India Institute of Medical Sciences, New Delhi, India of 402 patients with chronic pancreatitis with 3967 person-years of exposure, five patients developed pancreatic cancer (four with idiopathic, and one with hereditary chronic pancreatitis) after 16.60 ± 3.51 years of chronic pancreatitis (since diagnosis), giving a standardized incidence ratio of 121 (95% CI = 39.7–295.9) .[61] In a separate case-control study, 24 of 249 patients with pancreatic cancer had idiopathic chronic pancreatitis (none had alcohol-related pancreatitis) at a mean age of 45.6 ± 12.2 years, which gave an odd ratio of 97.7 (95% CI, = 12.7–751.4) compared to 1000 healthy controls after multivariable analysis .[62] In this study the proportion of patients with pancreatic cancer and underlying chronic pancreatitis who had a *SPINK1* variant (61.5%; 16 of 26 patients) was not significantly different from the proportion of patients with idiopathic chronic pancreatitis in the cohort study who had a *SPINK1* variant (47.8%; 32 of 67 patients).[62]

Question 2: What are the best available surveillance methods?

Statement 2.1: The best available surveillance methods are CT and MRI.

Quality assessment: Weak; Recommendation: Conditional; Agreement: **(α= 70%).**

Statement 2.2: EUS should not be used for surveillance as early tumors may be obscured by inflammation, fibrosis and calcification.

Quality assessment: Moderate; Recommendation: Weak; Agreement: **(α= 52%).**

Comment

There are no standard methods available for screening for early pancreatic cancer, even in high risk individuals. Therefore, surveillance would need to be undertaken using standard diagnostic techniques. Pancreas specific dual contrast multi-slice computed tomography (CT) is particularly useful in the diagnosis of pancreatic tumors.[44,63,64] Magnetic resonance imaging (MRI) and magnetic resonance cholangio-pancreatography (MRCP), with or without secretin stimulation of pancreatic duct flow can also be used to identify pancreatic cancer.[65-69] Endoluminal ultrasonography (EUS) is useful in helping to identify early pancreatic cancer against a normal pancreatic parenchyma. Identifying pancreatic cancer in the background of chronic pancreatitis is more difficult and early cancer may not be distinguishable against a background of parenchymal fibrosis and calcification in chronic pancreatitis.[70-72] CT can be performed in general hospitals with no access to EUS or MRI and is less time consuming and a cheaper alternative than most secondary investigations.[44] Whilst evidence for the use of EUS in surveillance for early pancreatic cancer that is curable in chronic pancreatitis is lacking, it is established as a diagnostic tool in cases of a suspicious lesion, although surgical resection remains the final option.[52,73-78]

Question 3: Where should surveillance for pancreatic cancer in patients with hereditary pancreatitis due to *PRSS1* mutations be undertaken?

Statement 3.1: Surveillance for pancreatic cancer in patients with hereditary pancreatitis due to *PRSS1* mutations should be undertaken in pancreatic specialist centers.

***Quality assessment: Low; Recommendation: Strong; Agreement:* (α= 100%).**

Comment

At the Fourth International Symposium of Inherited Diseases of the Pancreas in Chicago 2003 a key recommendation was that testing for PDAC in high risk groups should be performed only within the context of peer-reviewed protocols.[79] Pancreatic specialist canters are best

positioned to have experience in the progressive development of the optimum and most pragmatic approaches to screening and surveillance.[80] Leading centers can centralize registries and promote surveillance for participating centers at a national level such as the National Familial Pancreas Tumor Registry (NFPTR) established at Johns Hopkins in 1994 by Ralph Hruban, and EUROPAC established at Liverpool in 1996 by John Neoptolemos.[81] There is increasing interest in using endoscopic duodenal lumen juice aspiration to detect premalignant changes in the main pancreatic duct.[82-83]

Question 4: When should surveillance be initiated and stopped in hereditary pancreatitis?

Statement 4.1: Surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention.

Quality assessment: Moderate; Recommendation: Strong; Agreement: **(α= 97%).**

Comment

The largest series of patients with hereditary pancreatitis and pancreatic cancer is from EUROPAC, 26 (6%) patients diagnosed with pancreatic cancer out of 418 affected patients, with the risk increasing from the age of 40 years onwards.[22] A similar increase in risk from 40 years was reported by the APA and the IAP study with eight patients with pancreatic cancer from a cohort of 246 patients.[19] The study by Shelton *et al* with 217 *PRSS1* carriers (181 symptomatic) identified pancreatic cancer in five individuals, three symptomatic carriers and in two asymptomatic carriers, at a median age of death of 69 years with a range of 51-76 years.[22] A study from the German Registry of Hereditary Pancreatitis in Leipzig and Munster University in Germany reported on 101 subjects with *PRSS1* mutations (75 symptomatic). Only three of these patients were diagnosed with pancreatic cancer, with a median of 23 years (range 10-33) years after the onset of pancreatitis.[21] This was a 'snap-shot' study without prospective follow-up and included 25 patients who had had pancreatic surgery, out of 75 symptomatic

patients.21 In a recent study from India of 402 patients with chronic pancreatitis from any cause, there were five cases with pancreatic cancer diagnosed at a mean age of diagnosis of 50.9 years with a standard deviation of 10.1 years.[62]

To address the threshold for screening given as 40 years of age, the risk of missing a case of pancreatic cancer and the cost benefit of screening higher risk individuals must be balanced. Lowenfels *et al* followed 497 Hereditary Pancreatitis patients observing 19 pancreatic cancer cases, only three of whom developed pancreatic cancer before the age 40 and all three were smokers.[85] Suggesting little benefit of beginning screening before the age of 40, at least in non-smokers.

The frequency of surveillance will depend on the protocol being followed and may be modified according to molecular testing. There is no specified age to cease surveillance, as the risk continues to rise with age.[19-22] A simple guide is to consider stopping surveillance when the patient has such a fall in performance status that they would not be able to have either curative surgical treatment and/or palliative chemotherapy if the diagnosis of PDAC was made.

Question 5: What advice should patients with chronic pancreatitis be given in managing their disease in order to reduce risk of developing PDAC?

Statement 5.1: Patients should be advised to avoid use of tobacco, not drink alcohol, have a balanced healthy diet containing daily fruit and vegetables with a high folate intake, whilst moderating the intake of red meat and taking some form of regular high physical exercise, altogether aiming to avoid obesity.

***Quality assessment: Moderate; Recommendation: Strong; Agreement:* (α= 91%).**

Comment

Measures that might help to reduce the progression of chronic pancreatitis, may also directly and indirectly help to reduce the risk from developing pancreatic cancer, namely avoiding

tobacco and alcohol consumption.[2] There are also additional risk factors for PDAC that may be divided into genetic risk factors and environmental risk factors.[16,17,86] Individuals at high risk for PDAC include individuals with hereditary pancreatitis, as well as those with strong family history of pancreatic cancer, or familial cancer syndromes that include pancreatic cancer.[16-19,22,40,41,80,86] Those at particularly high risk include those individuals with hereditary pancreatitis due to PRSS1 mutations and cancer causing germline mutations.[17,19,22,40,41,50,80] Risk factors and factors that are protective of PDAC are shown in Table 2.[86]

Brown *et al* estimated that lifestyle and environmental factors accounted for 31.5% of all pancreatic cancers in the UK in 2015.[87] The contribution of tobacco smoking is 20-30% of all PDAC cases, alcohol consumption >30 (3.75 units) g /day accounts for <10%, whilst the attributable fraction for obesity varies from 3% to 27%.[16,86,87] The top six of the twelve recommendations of the European Code against Cancer are directly relevant to helping to prevent pancreatic cancer (Table 3).[88] The USA NIH-AARP (American Association of Retired Persons) Diet and Health Study, identified 1,057 cases of PDAC from 450,416 participants aged 50–71 years who had completed a diet and lifestyle questionnaire (1995–1996) followed up to December 2003.[89] It was estimated that around 30% of PDAC cases were attributable to low healthy lifestyle scores that could have been prevented.[89]

DISCUSSION

The risk of pancreatic cancer might be reduced by measures introduced to minimize the progression of chronic pancreatitis such as cessation of smoking and alcohol consumption as well as prophylactic total pancreatectomy.[2,45-49,85] Thus, variations in the estimates of relative risk are in part explained by differences in ascertainment of incident cases and the study design including the method of follow up, as well the impact of intervention (life-style, and medical and surgical measures) in prospectively followed up cohorts. In addition, although the number

deaths from pancreatic cancer might be ascertained, the total number of cases might not necessarily be established.

There was a strong consensus that affected individuals with an autosomal dominant history of hereditary pancreatitis due to inherited, gain-of-function *PRSS1* mutations should undergo surveillance but not patients with CP associated with *SPINK1* p.N34S. The number of cancers associated with *SPINK1* p. N34S is quite small and with a very wide confidence interval warranting further prospective studies.[39] Surveillance in affected individuals with an autosomal dominant history of hereditary pancreatitis but without *PRSS1* mutations was only weakly supported. The cumulative risk in this group of patients was not dissimilar to the group with gain-of-function *PRSS1* mutations comprising 21 (19%) of the 418 affected individuals in the EUROPAC Registry, indicating the need for further studies.[22] There was only conditional agreement for surveillance in patients with CP associated with other germline mutations of *CFTR, CTRC, CPA1*, and *CEL* due to the low relative risk of pancreatic cancer. [30-38,53-60] The was conditional agreement that the best available surveillance methods were CT and MRI, and only weak agreement on the use of EUS as early tumors might be obscured by inflammation, fibrosis and calcification, and also there was a lack of any reported cases of early tumor detection in hereditary pancreatitis by EUS. There was strong agreement that surveillance for pancreatic cancer should be undertaken in pancreatic specialist centers, to be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention. There was strong agreement that patients should be advised to avoid use of tobacco, not drink alcohol, and advised about a balanced healthy diet.[86]

Altogether, we require better estimates of pancreatic cancer relative risk in CP, in different countries around the world, and we need more outcome information on prospective surveillance in hereditary pancreatitis. In addition, we need better overall disease models where the interaction of multiple risk factors and their cumulative or potentiating effects can

be defined and were guidance on the use of early detection biomarkers can be accurately defined.[90,91]

CONFLICT OF INTEREST

JPN reports grants from NUCANA, Stiftung Deutsche Krebshilfe and Heidelberger Stiftung Chirurgie all outside of the submitted work; DCW is co-founder of Ariel Precision Medicine and may have equity.

STATEMENT IS REQUIRED FROM EACH CO-AUTHOR: ICJME FORMS MUST BE COMPLETED.

Table 1: Summary of pancreatic cancer relative risk in patients with chronic pancreatitis.

Author, year	Type of review	Number of studies	Strata	Summary Relative Risk (95% CI)
Raimondi et al, 2010[12]	Meta-analysis (16124 cases)	12 case-control-studies 10 cohort studies	Pancreatitis, unspecified Chronic pancreatitis Chronic pancreatitis (> 2 years) **Hereditary pancreatitis** **Tropical pancreatitis**	5.1 (3.5-7.3) 13.3 (6.1-28.9) 5.8 (2.1-15.9) **69.0 (56.4-84.4)** **100. (37.0-218.)**
Duell et al, 2012[13]	Pooled analysis (5048 cases)	10 case-control studies	Pancreatitis not otherwise specified (> 2 years)	2.71 (1.96-3.74)
Kirkegård, et al 2017[14]	Meta-analysis (4098 cases)	4 case-control studies 9 cohort studies	No lag period 1-year lag period 2-year lag period 5-year lag period Minimum 9-year lag period	7.96 (2.36-26.9) 6.09 (3.79-9.79) 16.16 (12.6-20.7) 7.90 (4.26- 14.7) 3.53 (1.69-7.38)
Tong et al, 2014[15]	Meta-analysis (14667 cases)	14 case-control studies 3 cohort studies	Pancreatitis Chronic pancreatitis Acute pancreatitis Diagnosis within 1 year Diagnosis for no less than 2 years Diagnosis for no less than 5 years Diagnosis for no less than 10 years	7.05 (6.42-7.75) 10.3 (9.13-11.7) 2.12 (1.59-2.83) 23.3 (14.0-38.9) 3.03 (2.41-3.81) 2.82 (2.12-3.76) 2.25 (1.59-3.19)

Table 2. Risk and protective factors for pancreatic cancer. *Factors that are amenable to primary prevention are highlighted. Modified from Maisonneuve and Lowenfels.[86]

High Risk **Relative risk >2.0**	**Moderate Risk** **Relative risk =1.5-2.0**	**Low Risk** **Relative risk =1.1-1.5**	**Protective** **Relative risk <1.0**
Hereditary pancreatitis Relative risk = 10-70	Family history Relative risk = 1.8	Metabolic syndrome Relative risk = 1.5	***Fruits and vegetables** Relative risk = 0.7
Germline mutations Relative risk = 5-30	Long-term diabetes mellitus Relative risk = 1.8	Helicobacter pylori Relative risk = 1.5	***High dietary folate** Relative risk = 0.7
Chronic pancreatitis Relative risk = 5-10	***Tobacco smoking** Relative risk = 1.7	***Obesity** Relative risk = 1.3	Atopic Allery Relative risk = 0.7
		Non-O blood group Relative risk = 1,3	***High physical activity** Relative risk = 0.9
		***Alcohol > 30g (3.8 units) per day** Relative risk = 1.2	
		***Red meat consumption** Relative risk = 1.2	

Table 3. The top six of the twelve recommendations of the European Code against Cancer to prevent cancer: directly relevant to pancreatic cancer prevention.[88]

Recommendations
1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet: • Eat plenty of whole grains, pulses, vegetables and fruits. • Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks. • Avoid processed meat; limit red meat and foods high in salt.
6. If you drink alcohol of any type, limit your intake.

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